REMARKS

Claims 1-2, 6, 11-12, 14-15, 20, 32-33, 35 and 38 have been amended to improve grammar and/or formatting.

Claims 22 and 30 have been amended to recite "identified" rather than "obtainable," support for which can be found in original claim 1.

The claims have been amended to more clearly describe the present invention, and no new matter has been added.

Applicants take this opportunity to thank the Examiner for the courtesies he extended in the interview of August 24, 2006. The enablement of claims 22-23, 25-31 and 39-40 was discussed, but no conclusion was reached.

1. Claim Rejections under 35 USC §112, First Paragraph – Enablement

The Examiner has rejected claims 22-23, 25-31 and 39-40 as allegedly failing to satisfy the enablement requirement (Office Action, pages 2-5). The Examiner relies on three lines of reasoning for imposing these rejections:

(a) the proper order and context of CDRs from both heavy and light chains being required for antigen binding;
(b) the selection of at least three CDRs from those set forth in SEQ ID NOs 61, 63, 65, 67, 69, 71, 73 and 75 amounts to an undue experimentation problem; and
(c) the failure of claim 22 to recite the predetermined epitope when the selected binding domain is known amounts to an undue experimentation problem.

In the following sections, Applicants respectfully traverse each aspect of the Examiner's rational for the enablement rejection.

2(a) The Proper Complement and Context of CDRs from both H and L Antibody Chains

The Examiner contends it is well established in the art that the proper context and complement of all three CDRs from both heavy and light antibody chains are required for antigen binding by an antibody (Office Action page 4). Applicants submit that the Examiner at least partially mischaracterizes what is known in the art. As a preliminary matter, Applicants agree it is well established that mammalian antibodies endowed with their full battery of CDRs from both heavy and light chains in their native context bind their target antigens. Applicants emphasize, however, that such a natural and full battery of mammalian-style CDRs is not necessary for binding a target antigen.

Applicants call the Examiner's attention to the fact that it is well known that certain species of cartilaginous fish have homodimeric immunoglobulins in which the variable domains recognize antigens with only a single, heavy chain-like immunoglobulin domain that contains only two (not three) CDRs. Despite this reduction in CDR number, such immunoglobulins still bind target antigen with nanomolar affinity (see the enclosed article by Stanfield et al., *Crystal structure of a shark single-domain antibody V region in complex with lysozyme*. 2004 Sep 17;305(5691):1770-3). **Applicants submit that this publication establishes as known in the art that a full battery of 3 CDRs from both the heavy and light chains of an antibody is not required for antigen binding**.

Turning to the "context" aspect of this rejection, Applicants point out that it is well known that, in nature, epitope binding domains are located at the extreme N-terminus of an antibody, and epitope binding domains identified by traditional methods typically lose their binding function when positioned C-terminally of amino acid sequences or protein domains: *e.g.* in the context of a recombinant polypeptide (Specification, page 3 lines 1-9). In contrast, the epitope binding domains of the present invention bind their target epitope whether position C-terminally, N-terminally or in the middle of peptide sequences. Accordingly, a novel and nonobvious advantage of the epitope binding domains of the present invention is their ability to be used to generate bivalent and multivalent recombinant polypeptides (Specification page 1, paragraph 1; page 2, last sentence; and the Examples). **This disclosure by Applicants in their originally filed Specification establishes**

that the presently claimed epitope binding domains need not be in their native context in order to bind antigen.

While Applicants are not bound by any particular theory, it is believed that the unique features of the instant epitope binding domain identification process contribute to the presently claimed epitope binding domains' ability to bind antigen in virtually any context. Here, Applicants point out that the presently claimed epitope binding domains are selected for antigen binding when positioned internally in a recombinant polypeptide: *i.e.* in between the N-terminal blocking domain and C-terminal anchoring domain of the present invention.

In view of the foregoing points, Applicants submit that the state of the art and Applicants' disclosure in their Specification clearly teach a person of ordinary skill in the art how to make and use the presently claimed epitope binding domains without undue experimentation. Accordingly, Applicants submit that this aspect of the enablement rejection is improper, and respectfully request its reconsideration and withdrawal.

2(b) The Selection of at Least Three CDRs

The Examiner also contends that the selection of at least 3 CDRs from those set forth in SEQ ID NOs 61, 63, 65, 67, 69, 71, 73, 75 and 75 would impose undue experimentation problems (Office Action, page 3). The Examiner states that:

> *...choosing at least three from the pool of the SEQ Ids, and each CDR H or CDR L fragment may involve conformation change, would impose undue experimentation. It is because antigen-antibody binding is a delicate relationship requiring "latch-lock" perfect fitting. Randomly selecting any three of the regions, ranging from CDR H(1-3) of any SEQ ID to CDR L (1-3) of any SEQ ID, would not meet this "latch-lock" fitting relationship* (Office action, paragraph bridging pages 3-4).

Applicants submit that the Examiner again at least partially misconstrues what is known in the art and the present invention. Here, Applicants point out that many, but not all, protein domains are

known to be modular in nature (*i.e.* their primary amino acid sequence folds and/or assembles into the proper and active three-dimensional structure regardless of what position they occupy in a protein). Such modular domains can therefore be moved around in recombinant and chimeric proteins while maintaining function. By way of example, Applicants call the Examiner's attention to reporter proteins such as the green fluorescent protein (GFP) or beta-galactosidase. These proteins, or subdomains of them, are well known to be functional in a variety of recombinant and chimeric protein contexts.

As discussed above, antibody epitope binding domains are located at the extreme N-terminus of an antibody in nature, and epitope binding domains identified by traditional methods typically lose their binding function when positioned C-terminally of amino acid sequences or protein domains. Accordingly, epitope binding domains identified by traditional methods were not modular in nature. It is a novel and nonobvious aspect of the present invention to provide modular epitope binding domains. Again, Applicants call the Examiner's attention to the fact that epitope binding domains of the present invention bind their target epitope whether position C-terminally, N-terminally or in the middle of peptide sequences. (Specification page 1, paragraph 1; page 2, last sentence; and the Examples).

While Applicants are not bound by any particular theory, it is submitted that each CDR of an epitope binding domain generally makes an additive contribution to target epitope affinity of the presently claimed epitope binding domains, regardless of its context in a recombinant polypeptide or epitope binding domain. A POSITA, therefore, would not be burdened with undue experimentation in selecting at least three CDRs from those set forth in SEQ ID NOs 61, 63, 65, 67, 69, 71, 73, 75 and 75 in creating an epitope binding domain according to the present invention. For theses reasons, Applicants submit that this aspect of the enablement rejection is improper as well, and respectfully request its reconsideration and withdrawal.

2(c) The Failure of Claim 22 to Recite the Predetermined Epitope

The Examiner has rejected claim 22 as allegedly not enabled because it fails to recite the predetermined epitope when the selected binding domain is known (Office Action, page 4). Applicants respectfully traverse.

Applicants point out that the Examiner is reading into the claim limitations that do not exist. In particular, the Examiner states:

> The selected binding domain comprise the selected SEQ ID cannot bind to ANY predetermined epitope (Office Action, page 4).

Nowhere, however, does claim 22 recite that its epitope binding domains bind to "ANY" predetermined epitope, rather "a" predetermined epitope is recited. Applicants further submit that claim 22 is a product claim, not a method claim as the Examiner contends. The epitope bound by the epitope binding domains of claim 22 is an inherent property, and no enablement problem therefore exists.

In view of the above-presented remarks and amendments, Applicants submit that each and every aspect of the Examiner's enablement rejection is overcome, and therefore respectfully request its full withdrawal.

2. Claim Rejections under 35 USC §112, Second Paragraph – Definiteness

The Examiner has rejected claims 1, 21 and 22 as allegedly indefinite. Applicants respectfully traverse.

2(a) The Location of the Epitope Binding Domain in Claims 1 and 21

The Examiner contends that it is not clear whether the epitope binding domain is within the recombinant polypeptide in claims 1 and 21 (Office Action, page 5). Applicants point out that

claims 1 and 21 specify that the claimed recombinant polypeptides are comprised of an N-terminal blocking domain located at the N-terminus of the recombinant polypeptide, a C-terminal anchoring domain located at the C-terminus of the recombinant polypeptide and an epitope binding domain positioned between the N-terminal blocking domain and the C-terminal anchoring domain. It follows that the epitope binding domain must be located within the recombinant polypeptide, and the claim is therefore definite.

2(b) The Placement of the Predetermined Epitope in Claim 1

The Examiner contends that the method of claim 1 needs to place the predetermined epitope into the display system (Office Action, page 5). Applicants submit it is well established in the art that an inherent aspect of the instant biological display systems is the presentation of a predetermined epitope in a manner appropriate to the display system. Applicants submit that a POSITA, in light of his knowledge as such and the disclosure of Applicants' Specification, would immediately realize how and where the predetermined epitope fits into the claim 1 method for identifying the epitope binding domains of the invention. Accordingly, Applicants submit that the claim is definite.

2(c) The Identity of the Epitope Binding Domain in Claim 1

The Examiner contends that it is not clear that the identified recombinant polypeptide is the epitope binding domain (Office Action, page 5). Claim 1 has been amended in a manner believed to overcome the Examiner's objection.

2(d) Obtainable in Claims 22 and 30

The Examiner contends that "obtainable" in claims 22 and 30 is vague and indefinite(Office Action, page 5). Applicants have amended these claims according to the Examiner's suggestion, thereby obviating the rejection.

2(e) "Set Forth In" – Claims 32, 33 and 35

The Examiner contends that the language "set forth in" implies "fragments," and concludes that the meets and bounds of claims 32, 33 and 35 are therefore unclear (Office Action, page 5). These claims have been amended in a manner believed to overcome the Examiner's objection.

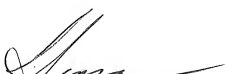
In view of the above-presented amendments and remarks, Applicants respectfully request reconsideration of the rejections and allowance of the claims.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 
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